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EXAMINER	
LEAVITT, MARIA GOMEZ	
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1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,764	JAVITT, NORMAN B.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-26* is/are pending in the application.

4a) Of the above claim(s) *23-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Applicants' response to the Office Action of 09-11-2007 has been entered. Claims 21-26 are pending. Claims 1-20 have been canceled by Applicants' amendment filed on 12-14-2007. Newly submitted claims 21-26 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: original claim 17 of the elected invention, now canceled, was drawn to a screening method for identifying agents compounds capable of interfering with the expression of 27-hydroxy-7-dehydrochlosterol reductase activity comprising determining the levels of 27-hydroxy-7-dehydrochlosterol reductase protein or its encoding mRNA wherein an agent that reduces expression of 27-hydroxy-7-dehydrochlosterol reductase protein or its encoding mRNA is identified as an agent able to reduce 27-hydroxy-7-dehydrochlosterol reductase activity. New **claim 21,** in part, is drawn to a method for identifying agents capable of increasing levels of 27-hydroxy-7-dehydrocholesterol (cholesta-5,7-diene-3β-27 diol) and/or 27-hydroxy-8-dehydrocholesterol (cholesta-5,8-diene-3β-27 diol) by measuring levels of 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol. Similarly, new **claim 23** is drawn to a method for identifying agents capable of increasing levels of 27-hydroxy-7-dehydrocholesterol (cholesta-5,7-diene-3β-27 diol) and/or 27-hydroxy-8-dehydrocholesterol (cholesta-5,8-

diene-3β-27 diol) comprising determining levels of 27 hydroxylase by measuring mRNA CYP277 encoding 27 hydroxylase. Further, new **claims 24-26** are drawn to a method for identifying agents capable of increasing the level of 7 hydroxylase by determining levels encoding mRNA CYP7. A restriction requirement was made in this invention. Applicants elected to prosecute in the response filed on 02-22-2007 Group IV, claims 16-17, drawn to a method of screening a compound. The election was treated as an election without traverse. Additionally, Applicants elected with traverse in the response to a supplemental restriction filed on 06-11-2007, the invention of Group II, claim 17, which is drawn to a method for identifying agents capable of interfering with the expression of **27-hydroxy-7-dehydrocholesterol reductase activity** by measuring RNA expression. Thus, new claims 21 in part, 23 and 24-26 do not correspond to the elected invention, accordingly, claims 23 and 24-26 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Therefore, **claim 21** to the extent the it reads on methods for identifying a compound that interferes with the expression of 27-hydroxy-7-dehydrochlosterol reductase activity and **claim 22**, drawn to a method for identifying agents capable of interfering with the expression of 27-hydroxy-7-dehydrochlosterol reductase activity are under current examination to which the following grounds of rejection are applicable .

Response to arguments

Withdrawn Rejections/Objections in response to Applicant arguments or amendments

Abstract

In view of Applicants' amendment of the disclosure in the abstract to mention a major embodiment of the instant invention drawn to methods for screening and/or assaying agents capable of inhibiting 27-hydroxy-7-dehydrochlosterol reductase, objection to the abstract has been withdrawn.

Rejections/Objections maintained in response to Applicant arguments or amendments

Specification

The disclosure remains objected to because of the following informalities: the brief description of the drawings in the specification has been amended at page 7, paragraphs [0026]-[0028], however the amended brief description of the drawings does not reflect the content of Figures 1-7 on the 3 pages of the original drawings submitted on 9-10-03.

Moreover, the examiner notes that no replacement drawings have been submitted, contrary to Applicants' assertion at page 8 of the Remarks filed on 12-14-2007.

Claim Rejections - 35 USC § 112

The rejection of claim 17, now canceled, under 35 U.S.C. 112, first paragraph, is maintained over new claim 22 for the reasons of record as discussed in detail in the paragraphs below.

New claims 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Response to Applicants' Arguments as they apply to rejection of 21-26 under 35 USC § 112- First paragraph- Enablement.

At page 8 of Remarks, Applicants argue that "now present new claims 21-26 which more clearly and particularly set out and claim screening methods. In particular and in accordance with the above claims, the claims as amended and now presented relate generally to screening methods for agents/compounds capable of increasing 27-hydroxy-7-dehydrocholesterol (cholesta-5,7-diene-3β-27 diol) and/or 27-hydroxy-8-dehydrocholesterol (cholesta-5,8-diene-3β-27 diol)". Additionally, Applicants contend that "this more clearly describes and relates to the desired physiological result, an increase in the 27- hydroxy metabolites of 7-dehydrocholesterol or 8-dehydrocholesterol, and that these methods are fully enabled by the specification", because the 27-hydroxy metabolites of 7-DHC or 8-DHC may be increased by interfering with or inhibiting the 27-hydroxy-7- dehyrodrocholesterol reductase or stimulating 27-hydroxylase activity". Such is not persuasive.

The scope of the invention as embraced by claim 22 is not commensurate with the disclosure of the as filed evidence for the reasons of record and the following reasons. A large embodiment of the instant application is drawn to a screening method for identifying agents capable of interfering with expression of 27-hydroxy-7-dehydrochlosterol reductase activity, which identifies compounds capable of increasing 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol (27-hydroxy metabolites of 7-DHC and/or 8-DHC) levels, wherein the expression of 27-hydroxylase, as determined by measuring its encoding mRNA CYP27 is not altered. Applicants have not provided sufficient disclosure in relation to the 27-hydroxy-7-dehydrocholesterol reductase, nor isolated the reductase enzyme, nor produced

antibodies specific for recognizing the enzyme, nor isolated the cDNA of the enzyme from a library in order to show that applicants by measurement of mRNA level of CYP27 encoding the 27 hydroxylase may increase 27-hydroxy metabolites of 7-DHC and/or 8-DHC levels and thus identify a compound that interferes with expression of 27-hydroxy-7-dehydrocholesterol reductase. Applicants merely provide one example wherein levels of cholesterol intermediates including 27-hydroxy-7-dehydrocholesterol and 27-hydroxy-8-dehydrocholesterol are measured from samples of patients with SLOS (Smith-Lemli-Opitz syndrome), but not the enzyme responsible for the intermediate production. Hence, applicants measure levels of downstream products of such a reductase, but not the reductase directly. Further, the specification is silent about any data correlating expression of 27-hydroxylase as determined by measurement of mRNA level of CYP27 and increased levels of 27-hydroxy metabolites of 7-DHC and/or 8-DHC and thus identification of a test compound that interferes with the 27-hydroxy-7-dehydrocholesterol reductase activity. Applicants have not provided the nucleic acid sequence of such a reductase, or the oligo sequences of primers that might be used to such detection. Applicants have provided no nucleic acid sequences within the body of the specification, nor pointed to a Genbank or published article in which such sequences might appear. The skilled artisan would be required to first identify, isolate, and reproduce the 27-hydroxy-7-dehydrocholesterol reductase in order to practice the claimed invention. Expression studies, in which tissues the reductase is expressed in, the regulation of the reductase and its relation to expression levels of 27 hydroxylase in the pathway leading to synthesis of cholesterol, potential evaluation of reductase isoforms, *in vivo* evaluation of elevated 27-hydroxy metabolites of 7-DHC and/or 8-DHC levels and identification of a compound interfering with 27-hydroxy-7-

dehydrocholesterol reductase activity would all be required to be performed in order for the skilled artisan to make and use the claimed invention.

At page 8 of Remarks, Applicants argue that "In addition, increasing 7- hydroxylase results in more 7-dehydrocholesterol, thereby providing more substrate for 27- hydroxylation to form 27- hydroxy-7-dehyrodrocholesterol. Thus, specific such screening methods are now presented, which Applicants assert are fully enabled by the Specification, taking into consideration the extensive and significant skill of the skilled artisan and applying the Wands factors". Such is not persuasive.

At the outset, the examiner disagrees with Applicants' position that "increasing 7-hydroxylase results in more 7-dehydrocholesterol thereby providing more substrate for 27-hydroxylation to form 27- hydroxy-7-dehyrodrocholesterol". Though hydroxylation of cholesterol by 7-α-hydroxylase leads to 7-hydroxylation C7α and production of 7 α-hydroxycholesterol to form primary bile acids by co-action of CYP7A and CYP7B (see, Lathe et al., 2002, Steroids, 967-97; p. 968; Specification, page 5, paragraph [0020]), it is unclear how 7-hydroxylation by 7-hydroxylase leads into a pathway that generates 7-dehydrocholesterol and not 7- α-hydroxycholesterol, let alone the pathway by which 7-dehydrocholesterol is a substrate for 27- hydroxy-7-dehyrodrocholesterol. Because applicants have provided no data on the existence of a 27-hydroxy-7-dehydrocholesterol reductase other than the identification of the 27-hydroxy-7-dehydrocholesterol product (i.e., 27-hydroxy metabolites of 7-DHC and/or 8-DHC), the skilled artisan would have to perform trial and error in order to actually produce the enzyme, either in protein or nucleic acid form, in order to then practice the claimed invention and measuring either levels of 27-hydroxy metabolites of 7-DHC and/or 8-DHC or unmodified levels

of 27 hydroxylase mRNA, in order to effectively determine the correlation of elevated levels of 27-hydroxy metabolites of 7-DHC and/or 8-DHC or levels of 27 hydroxylase mRNA effecting expression of the 27-hydroxy-7-dehydrocholesterol reductase activity.

Claim Rejections - 35 USC § 112

The rejection of claim 17, now canceled, under 35 U.S.C. 112, second paragraph, is maintained over new claims 21 and 22 for the reasons of record as discussed in detail in the paragraphs below.

Claims 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. New claims 21 and 22 are directed towards a screening method for identifying agent compounds capable of interfering with the expression of 27-hydroxy-7-dehydrocholesterol reductase activity, in part by determining the expression of 27 –hydroxylase and its level of non altered CYP27 mRNA. The specification is silent about what enzyme is being measured. Therefore it is unclear whether expression of 27 –hydroxylase results in 27-hydroxylation of the 27-hydroxy-7-dehydrocholesterol reductase and/or 27-hydroxy metabolites of 7-DHC and/or 8-DHC. Moreover, it is unclear from the specification and the claim what enzyme is being measured, either direct measurement of elevated 27-hydroxy metabolites of 7-DHC and/or 8-DHC levels, or 27-hydroxylase encoding mRNA? A skilled artisan would be unable to determine the metes and bounds of the claimed invention.

New Grounds of Rejection

Claim Rejections - 35 USC § 112- First paragraph- New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 recites a screening method for identifying agent compounds " wherein said compound interferes with the expression of 27-hydroxy-7-dehydrocholesterol reductase activity or stimulates expression of 27-hydroxylase activity" and claim 22 recites "a compound capable of increasing 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol levels wherein the expression of 27-hydroxylase, as determined by measuring its encoding mRNA CYP27, is not altered". The specification as filed teaches at page 1, paragraph [0005], that "a reduced level of 27-hydroxycholesterol in the serum was found to be associated with cholesterol build up in the tissues; thus, the administration of 27-hydroxycholesterol was proposed as a method for reducing the rate of cholesterol synthesis in the body… … . Individuals with a genetic defect in producing 27-hydroxycholesterol exhibit accelerated atherosclerosis and die early in life of severe coronary artery disease. The molecular basis of this genetic disease is a mutation in the CYP 27 gene, which results in a lack of cholesterol 27-hydroxylase activity". No other teachings are disclosed of "a compound capable of increasing 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol levels wherein the expression of 27-hydroxylase, as determined by measuring its encoding mRNA CYP27, is not altered". Thus is not clear that the Applicant was in possession of a genus of undefined compounds "capable of increasing 27-hydroxy-7-dehydrocholesterol and/or 27-hydroxy-8-dehydrocholesterol levels

wherein the expression of 27-hydroxylase, as determined by measuring its encoding mRNA CYP27, is not altered" at the time the application was filed.

Conclusion

Applicant response filed on 12-14-2007 has been considered by the Examiner but has not been found persuasive in view of the new grounds of the rejection, which is necessitated by the claims amendment.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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